



## **A comparative study between using of Fentanyl- Ketamine and Xylazine- Ketamine combinations as anaesthetic regmine in rabbits.**

Wisam. H. S. AL-Shebani      Haydar A. N. AL-Zamely      Noora. K. H. AL-Yasari  
College of Vet- Med.      College of Vet- Med.      College of agriculture  
University of Al-Qadisiya      University of Al-Qadisiya      University of Al-Qadisiya

### **Abstract**

The anaesthetic and some cardiopulmonary effects of Fentanyl- Ketamine (FK) and Xylazine- Ketamine (XK) combinations were studied and compared in rabbits. A sixteen rabbits were randamoly assigned to (2) different group FK and XK groups. The rabbits in FK group (n=8) were injected 0.02 mg/ kg B. W of fentanyl and 40 mg/ kg B. W of ketamine. The XK group was given 4 mg/ kg B. W of xylazine and 40 mg/ kg B. W of ketamine. All drugs in two different groups were mixed in one syringe and injected intramuscularly. Respiratory and heart rates were recorded at 2 minute before anaesthesia and 5, 10, 15, 30, 45, 60, 75, 90 and 120 minute after anaesthesia. Both groups showed depression in respiratory and heart rates after administration of anaesthetic agent, but the depression in respiratory rates in FK group was significantly more than in XK group at (5-60) minutes after injection ( $P<0.05$ ). While the depression in the heart rate in FK group was significantly lower than in XK group at (45-75) minutes after injection ( $P<0.05$ ). Data on reflexes (righting, pedal withdrwal for front and hind limb, ear pinch) were recorded to be utilized in determination of different stages of anaesthesia. Mean duration of loss of pedal withdrwal reflex for both front and hind limb and ear pinch reflex were significantly longer in the XF group than in the FK group ( $P<0.05$ ). The duration of surgical tolerance was significantly longer in XK group than FK group ( $P<0.05$ ). While the stage of early recovery and late recovery lasted significantly ( $P<0.05$ ) longer in XK group than in FK group. We concluded that anaesthesia with XK or FK was suitable for common surgical produce in rabbits and the providing of oxygen is recommended in order to overcome the hypoxia.

### **Introduction**

Rabbits are now the third most commonly anaesthetized pet (1). However, their pre- anaesthetic mortality rate (1 in 72) is still higher than that of dogs (1 in 601) (1).

There are number of surgical interventions such as dental procedures, castration and fracture repair should be performed under anaesthesia. Intubation of the rabbit and use of a volatile anaesthetic agent, possibly in combination with muscle relaxants, may be too complicated and time-consuming (2). As a result of these problems an injectable technique is needed for use in rabbits that gives adequet depth of anaesthesia and also a good quality and rapid recovery (3).

Several injectable drugs were used in rabbits as ketamine, which when use as a sole anaesthetic agent in rabbits it tends to cause hypertonus, poor



muscle relaxation, persistent pain, reflex responses and violent recovery from anaesthesia (4). Therefore, several drugs are combined with ketamine such as xylazine (well known  $\alpha_2$  agonist drug), in order to overcome ketamine side effects.

For the same previous reasons we used fentanyl, opioid agonist in combination with ketamine to potentiate the anaesthetic properties of ketamine in rabbits. The fentanyl has 80 times the analgesic potency of morphine and it used in anaesthesia (5), also it is widely used in veterinary medicine as its use to produce surgical anaesthesia in dogs (6) and satisfactory anaesthesia in rabbits after its combination with midazolam and medetomidine (7).

There is a need to perform study aimed to:

- 1- Evaluation the anaesthetic activity of fentanyl- ketamine combination and investigate its effect on some cardiopulmonary variables and then compare with xylazine- ketamine combination in rabbits.
- 2- Assessment of anaesthetic stages and depth by determination of certain reflexes in rabbits for the above two different combinations.

### Materials and Methods

#### Animals and drug dosage:

The study was performed on 16 adult rabbits of either sex with a mean of body weight  $2.02 \pm 0.21$  Kg. The rabbits were randomly assigned to (2) groups. The first was Fentanyl- Ketamine mixture (FK) group and the second was Xylazine- Ketamine mixture (XK) group. The rabbits in group FK (n=8) were given 0.02 mg/kg. B. W. I. M of fentanyl (F) (fentanyl-janssen, 0.05 mg/ml; Jassen pharmaceuticals) and 40 mg/kg. B. W. I. M of ketamine (K) (Tekam, 50 mg/ml; Hikma pharmaceuticals, Aman, Jordan). In group XK the rabbits were given 4 mg/kg. B. W. I. M of xylazine (seton, 20 mg/ml, Laboratories Caller, Barcelona, Spain) and 40 mg/kg. BW I/M of ketamine. All drugs of the different combinations were mixed in one syringe and injected into the femoral quadriceps muscle. The animals were breathing room air during anaesthesia. A standard clinical examination proceeded general anaesthesia.

#### Parameters:

The following parameters were measured:

- 1- Assessment of some cardiopulmonary variables included:
  - *Respiratory rates (RR, breath/ minutes)*: based on counting thoracic movement (7).
  - *Heart rate (HR, beats/ minute)*: by using of stethoscope.

Baseline recordings of RR and HR were obtained at 2 minute before injection of drugs, then they were recorded at 5, 10, 15, 30, 45, 60, 75, 90 and 120 minute during anaesthesia.

- 2- Depth of anaesthesia was assessed by recording the presence or absence of the following reflex responses:



- *Righting reflex*: the animal showing the ability to spontaneously right itself after being placed on its back (8).
  - *Toe pinch reflex (pedal withdrawal reflex)*: in the front and the hind legs, pressure on the basis of the claw resulted in withdrawal of limb in response to claw pinching (9).
  - *Ear pinch reflex*: shaking the head or vocalization when the pinna was pinched using investigator's fingernails (8).
- 3- Evaluation of different stages and planes of anaesthesia: were assessed according to criteria suggested by Heneke et al., (10) explained as follow:
- *Stage of induction*: from time of injection (t=0) to completely loss of righting reflex.
  - *Stage of hypnosis*: from loss of righting reflex to loss of toe- pinch reflex in front and hind legs and loss of ear- pinch reflex.
  - *Stage of surgical tolerance (Surgical anaesthesia)*: from loss of toe pinch reflex in front and hind legs and loss of the ear- pinch reflex to smooth recurrence of ear- pinch reflex.
  - *Stage of early recovery*: from smooth recurrence of ear- pinch reflex to recurrence of toe- pinch reflex at front and hind legs and more forceful ear- pinch reflex.
  - *Stage of late recovery*: from recurrence of toe- pinch reflex in front and hind legs and even more forceful ear- pinch reflex to recurrence of righting reflex.

### Results and Discussion

**Table (1) Respiratory and heart rates perminute (Mean ± SE) for rabbits after injection of FK or XK combination.**

Time (minute)	RR (breaths/ minute)		HR (beats/ minute)	
	FK group	XK group	FK group	XK group
0	188.25±4.25	186.12±7.51	198±5.32	202.25±5.49
5	36.25±2.09	49±5.08 *	200±9.68	189.12±6.07
10	31±2.32	45±2.76 *	185.87±7.25	178.75±9.15
15	27.25±1.66	40±2.11 *	182.12±3.96	170.87±9.36
30	24.25±1.71	32.12±2.58 *	180.37±4.78	155.12±11.82
45	22.87±2.15	37.62±3.50 *	186.62±6.54	156±8.98 *
60	34.25±2.95	45.25±3.26 *	193±5.56	158±13 *
75	48.12±4.07	57±3.32	193.25±5.59	162±9.62 *
90	61.37±4.34	59.87±4.74	192.62±9.908	162.87±10.23
120	63.25±1.77	61.62±2.84	194±14.90	162.37±11.80

\*: The values are highly significant at (P<0.05) performing t. test.



All rabbits were tachypnoeic before induction, the RR varying between  $188.25 \pm 4.52$  and  $186.12 \pm 7.51$  breaths per minute, then became below the baseline value during anaesthesia in both groups. The RR in the FK group was significantly lower ( $P < 0.05$ ) compared with the XK group between 5 and 60 minutes after administration of drugs (table 1). The most prominent effects on respiration were seen in the FK group in which RR fell markedly, however the lowest RR during anaesthesia was  $22.87 \pm 2.15$  recorded in FK group at (45) minutes after administration of drug mixture. The short period of apnoea occurring in some animals in FK group could probably be attributed to the opioid constituent (10). It should be noted that the respiratory depression is not unique to the use of FK or XK, but also occurs with other injectable anaesthetic regimens in rabbits (11) and (3), therefore, it advisable to administer oxygen during anaesthesia.

Rabbits in both group of FK and XK showed lowest HR after injection of anaesthetic combinations (table 1). The  $\alpha_2$ - agonist are known to produce marked bradycardia (12). Therefore, the animals which received xylazine showed evidence of bradycardia. The extent of HR decreases in this study agrees with value reported by (13) and (14). Also it known that opioid causes bradycardia as a result of its stimulation to the vagal center (15).

Therefore, animals which received fentanyl also show bradycardia and this came in accordance with fact reported by (7) that fentanyl potentiate the fall in HR when mixed with other anaesthetic agents.

The significantly higher HR in the rabbits anaesthetized with FK compared with the rabbits anaesthetized with XK between 45 and 60 minutes could have been due to the shorter bradycardiac effect of fentanyl.

Although the stimulatory cardiovascular effects of ketamine are less marked in rabbits compared with other species (16), ketamine able to temporary counteract the breadycardia produced by fentanyl and xylazine.

**Table (2): The times (mean $\pm$  SE) of loss of the righting reflex, duration of loss of pedal withdrwal reflex (for front and hind limb) and duration of loss of ear pinch reflex, after injection of FK or XK mixture.**

Anaesthetic combination	FK	XK
Time to beginning of loss of righting reflex (minutes)	$2.87 \pm 0.29$	$2.25 \pm 0.36$
Duration of loss of pedal withdrwal reflex (for front limb)(minutes)	$26 \pm 1.26$	$39 \pm 1.45$ *
Duration of loss of pedal withdrwal reflex (for hind limb)(minutes)	$25 \pm 1.56$	$37 \pm 1.23$ *
Duration of loss of ear pinch reflex (minutes)	$24.37 \pm 1.77$	$34 \pm 1.32$ *



\* Values are highly significant ( $P < 0.05$ ) by performing t. test.

**Table (3): The duration (mean  $\pm$  SE) of anaesthetic stages (minutes)**

Anaesthetic stage	Anaesthetic Combination	
	FK	XK
Induction	4.5 $\pm$ 0.37	4 $\pm$ 0.32
Hypnosis	13.37 $\pm$ 0.84	12 $\pm$ 0.65
Surgical tolerance	15 $\pm$ 0.84	22 $\pm$ 0.80 *
Early recovery	14 $\pm$ 0.90	18 $\pm$ 0.65 *
Late recovery	37 $\pm$ 0.86	53 $\pm$ 1.52 *

\* Values are highly significant ( $P < 0.05$ ) by performing t. test.

The righting reflex was lost within (2.5-2.87) minutes in all rabbits, and the time to loss this reflex did not differ significantly between groups (table 2). The duration of ear pinching reflex was significantly greater in XK than FK. A similarly significant longer duration of both pedal withdrawal response in front and hind limb occurred with XK compared with FK.

Both of xylazine and fentanyl greatly potentiate the analgesic activity of ketamine in rabbit. There are interaction between opiate receptors and  $\alpha_2$ -adrenoceptors in the brain (17) and spinal cord (18). The  $\alpha_2$  and opiate receptors are found in similar regions of the brain and even on some of the same neurons. The  $\alpha_2$ - agonist and  $\mu$  opioid agonist produce analgesia by similar mechanism (12). As it showed by the results of present study the depth of analgesia in XK group is more potent than FK group.

When evaluating anaesthetic depth, after the fading of reflexes a positive response was sometimes seen when repeated stimulus was applied. The first stimulus seemed to arouse the rabbit to a state in which a repeated stimulus showing response (2). When evaluating the anaesthetic depth repeating the stimulation should be done because most surgical operation is repetitive nociceptive stimulation.

Induction and hypnosis stages of anaesthesia were generally smooth and duration did not differ significantly between groups. The duration of surgical tolerance was significantly longer in the XK group when compared with FK group. According to Wright, (19) the  $\alpha_2$ - agonist, xylazine, in the XK combination is responsible for this prolongation of the surgical tolerance. While the planes of early recovery and late recovery lasted significantly longer in XK group than in the FK group. Considering the duration of the entire anaesthesia period (time from injection of the anaesthetics to the re-occurrence of the righting reflex), a clearly marked prolongation of the recovery time could be seen in animals receiving the XK



combination which is in accordance with (20). The differences in duration of the various anaesthetic periods are presumably because of differences in the metabolism of the components.

A most common surgical procedure (e. g. dental procedures, castration) usually require only 15-30 minutes of surgical anaesthesia (10). An anaesthetic protocol including combination of XK or FK with oxygen supplement is appropriate to provide sufficient anaesthesia and intraoperative analgesia. We concluded that the XK mixture is more suitable anaesthetic regime in rabbits as it cause more anaesthetic depth and less respiratory depression compared to FK mixture, although FK mixture causes less depressant effect on HR.

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## دراسة مقارنة بين استخدام مزيجي

### الفنتانيل-الكيتامين والزايلازين - الكيتامين كبرامج تخدير في الارانب

نورة كاظم هادي اليساري	حيدر عبد الكاظم نغيش الزاملي	وسام حسين سلمان الشباتي
كلية الزراعة	كلية الطب البيطري	كلية الطب البيطري
جامعة القادسية	جامعة القادسية	جامعة القادسية

### الخلاصة

تم دراسة ومقارنة الفعل التخديري وبعض التأثيرات على القلب والتنفس لتوليفة الفنتانيل- الكيتامين الدوائية وتوليفة الزايلازين- كيتامين الدوائية في الارانب. تم استخدام (١٦) ارنب تم تقسيمها عشوائياً الى مجموعتين المجموعة الاولى مجموعة الفنتانيل- كيتامين عددها (٨) تم حقنها بـ ٠.٠٢ ملغم/ كغم من وزن الجسم بدواء الفنتانيل و ٤٠ ملغم/ كغم من دواء الكيتامين، المجموعة الثانية مجموعة الزايلازين- كيتامين عددها (٨) تم حقنها بـ ٤ ملغم/ كغم من وزن الجسم بدواء زايلازين و ٤٠ ملغم/ كغم من وزن الجسم من الكيتامين، تم مزج الادوية في كلا التوليفتين الدوائيتين في محقنة واحدة وحقنت بالعضل.

تم قياس عدد مرات التنفس وعدد ضربات القلب في الدقيقة قبل دقيقتين من اعطاء التخدير وبعد ٥، ١٠، ١٥، ٣٠، ٤٥، ٦٠، ٧٥، ٩٠، ١٢٠ دقيقة بعد اعطاء التخدير. اظهرت كلا المجموعتين تثبيطاً في عدد مرات التنفس وعدد ضربات القلب، لكن التثبيط في عدد مرات التنفس في مجموعة الفنتانيل- الكيتامين كان اكثر منه في مجموعة الزايلازين- الكيتامين خلال الفترة (٥-٦٠) دقيقة بعد الحقن حيث كان الاختلاف معنوياً وتحت مستوى احتمال ( $P<0.05$ )، بينما كان التثبيط في عدد ضربات القلب في مجموعة الفنتانيل- الكيتامين معنوياً اقل منه في مجموعة الزايلازين- الكيتامين خلال الفترة (٥-٧٥) دقيقة بعد الحقن وتحت مستوى احتمال ( $P<0.05$ ). تم تسجيل البيانات حول بعض المنعكسات (منعكس التصحيح، منعكس سحب القدم الامامية والخلفية، منعكس قرص الاذن) ليتم الاستفادة منها في تحديد مختلف مراحل التخدير. ان معدلات منعكس سحب القدم الامامية والخلفية ومنعكس قرص الاذن كانت معنوياً أعلى في مجموعة الزايلازين- الكيتامين منها في مجموعة الفنتانيل- الكيتامين وتحت مستوى احتمال ( $P<0.05$ ).

ان مدة التخدير الجراحي كانت اكثر في مجموعة الزايلازين- الكيتامين منها في مجموعة الفنتانيل- الكيتامين حيث كان الاختلاف معنوياً على مستوى احتمال ( $P<0.05$ )، كما وان مرحلتي الافاقة المبكرة والمتأخرة تأخرت معنوياً في مجموعة الزايلازين- الكيتامين اكثر منها في مجموعة الفنتانيل- الكيتامين وعلى مستوى احتمال ( $P<0.05$ ). تم الاستنتاج بأن التخدير بتوليفة الفنتانيل- الكيتامين او الزايلازين- كيتامين كان مناسباً لمعظم العمليات الجراحية الشائعة في الارانب مع الاخذ بنظر الاعتبار التوصية بتوفير الاوكسجين اثناء فترة التخدير للتغلب على مشاكل نقص التهوية المصاحبة للتخدير.